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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/645,085	10/07/2002	Naoshi Fukushima	065678-0108	7376

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EXAMINER

BRISTOL, LYNN ANNE

ART UNIT PAPER NUMBER

1643

DATE MAILED: 09/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	10/645,085	FUKUSHIMA ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 31 July 2006.
- 2a) ☒ This action is FINAL.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 1-17 and 20-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 18 and 19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                                    |                                                                             |
|----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____                                                |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>3/29/06; 4/25/06</u> .                                                    | 6) <input type="checkbox"/> Other: _____                                    |

### DETAILED ACTION

1. Claims 18 and 19 were amended in the Response of July 31, 2006.
2. On p. 11, at ¶1 of the Response, Applicant's citation to the specification for written support of the amendments of Claims 18 and 19 (p. 17, lines 20-21) has been considered, and the amendments have been entered.
3. Claims 1-22 are all the pending claims for this application.
4. Claims 1-17 and 20-22 are withdrawn from consideration.
5. Claims 18 and 19 are all the pending claims under examination.

### *Priority*

6. In response to Applicant's comments on p. 11, ¶2, the Examiner acknowledges that the certified copies of four Japanese language priority documents (PCT/JP01/01912, 2000-321822, 2000-321821, 2000-115246) declared in the Oath/Declaration and all cited as "foreign priority" documents in the original ADS were received upon National Stage entry for the instant application.
7. The Examiner acknowledges receipt of the certified translations for Japanese foreign priority documents 2000-321822, 2000-321821, 2000-115246, and that a certified translation of PCT/JP01/01912 has not been filed. However, none of these translations have been entered for reasons below.

The Examiner restates the Petitioner's Decision of August 25, 2003 granting the instant application a U.S. filing date of October 17, 2002 and a PCT filing date of April 17, 2001.

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It is noted that for each of the certified translations for JP 2000-321822, JP 2000-321821 and JP 2000-115246, the translation statement page identifies the U.S. filing date as "October 7, 2002".

Furthermore, in the supplemental ADS received with the Response of July 31, 2006, the U.S filing date for the instant application is also listed as "October 7, 2002", and Applicants have now changed their claim from foreign priority for PCT/JP01/01912 to domestic priority. Applicant's domestic priority claim to PCT/JP01/01912 under §365(c) is acknowledged and complies with the originally filed Oath/Declaration.

Thus because the certified translations for JP 2000-321822, JP 2000-321821 and JP 2000-115246 and the supplemental ADS do not identify the correct U.S. filing date, none of these documents have been entered or considered.

#### ***Information Disclosure Statement***

8. Applicant's requested the Examiner's consideration of an IDS filed on April 25, 2006 citing 74 references (p. 11, ¶13). It is noted that an IDS citing 74 references was actually filed on March 29, 2006. The referred IDS of April 25, 2006 cites only two references, whereas three documents were received with the filing. The Examiner has considered and entered all of the references enclosed at the time of respective filing with the exception of the document labeled "D3" (hand written notation) on the 1449 form of April 25, 2006. The one-page document received is untitled but appears to be a print-out from an international search authority from a related application.

***Objection(s) Maintained***

***Specification***

9. The objection to the specification is maintained. Applicants have not identified the text of the specification to be deleted (p. 92, line 12- p. 101, line 4) in their amendment of the specification to introduce a Brief Description of the Drawings at p. 4, line 5, prior to the "Disclosure of the Invention" (p. 11, ¶4). (MPEP 714).

***Rejections Withdrawn***

***35 USC § 112, second paragraph***

10. The rejection of Claims 18 and 19 under 35 U.S.C. 112, second paragraph, as being indefinite for omission of method steps is withdrawn in view of Applicant's arguments on p. 11 at ¶¶5 and 6 and the amendment of the claims to recite that the VH and VL regions are connected by linker of an amino acid length conducive to forming a dimer or a diabody as known in the art (e.g., Atwell et al. Protein Engineering 12(7):597-604 (1999)) and taught by the specification (p. 17, lines 20-21; Examples 5 and 6).

***35 USC § 112, first paragraph- scope of enablement***

11. The rejection of Claims 18 and 19 under 35 U.S.C. 112, first paragraph, as being non-enabled for methods of producing or stabilizing any dimer derived from just any host cell-expressed scFv in the presence of serum-free medium alone is withdrawn. Applicants' comments at p. 12, ¶1 and the claim amendments to recite the presence and length of the linker bring the claims into statutory compliance for enablement.

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**35 U.S.C. §103**

12. The rejection of Claim 18 under 35 U.S.C. §103(a) as being obvious over Kortt et al. (Protein Eng. 10:424-433 (1997) in view of Dorai et al. (Biotechnology (NY) 12(9):890-897 (1994) as evidenced by Verma et al. (J. Immunol. Methods 216:165-181 (1998) and further in view of Keen et al. (Cytotechnology 18:207-217 (1995) is withdrawn. Applicants' comments with respect to each of the references taken alone (p. 12, ¶13- p. 13, ¶1) or together (p. 13, ¶2) are found persuasive in overcoming this rejection.

***Rejections Maintained***

**35 USC § 102(e)**

13. The rejection of Claims 18 and 19 under 35 USC 102(e) as being anticipated by Fukushima et al (U.S. 20040073013; filed March 12, 2001; published June 12, 2003) is maintained.

Applicants' allege that the certified translations for the three Japanese priority documents would overcome the rejection over the Fukushima art reference (U.S. 20040073013) (p. 12, ¶2). It is noted that Fukushima claims priority to PCT/JP01/01912, JP 2000-115246 and JP 2000-321822, but not JP 2000-321821. Applicants have not identified the supporting text in any of the English language translations for the instant claims. Further, and as discussed supra, the documents have not been entered or considered.

**35 USC § 103(a)**

14. The rejection of Claim 18 under 35 U.S.C. §103(a) as being obvious over Fukushima et al. (WO 00/53634; filed March 10, 2000) in view of Kortt et al. (Protein Eng. 10:424-433 (1997) and further in view of Keen et al. (Cytotechnology 18:207-217 (1995) as evidenced by Verma et al. (J. Immunol. Methods 216:165-181 (1998) is maintained.

Applicants have not so much as addressed the Fukushima reference (WO 00/53634) alone or in combination with the secondary references in their response to the Office Action. The Fukushima reference does not claim priority to any of the Japanese priority documents for this application. Thus it is unclear what relevance any of the translations would have even if the Examiner were to apply them to the rejection over Fukushima et al. (WO 00/53634).

15. The rejection of Claim 19 under 35 U.S.C. §103(a) as being obvious over Reiter et al. (Biochemistry 33:5451-5459 (1994) in view of Dorai et al. (Biotechnology (NY) 12(9):890-897 (1994) as evidenced by Verma et al. (J. Immunol. Methods 216:165-181 (1998) and further in view of Keen et al. (Cytotechnology 18:207-217 (1995) is maintained.

Applicants have not so much as addressed the Reiter reference alone or in combination with the secondary references in their response to the Office Action.

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16. Applicants amendments to the claims have necessitated new grounds for rejection. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***New Grounds for Rejection***

***Claim Rejections - 35 USC § 112, second paragraph***

17. Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, for the following reasons:

a) Claims 18 and 19 are indefinite for the recitation "linker composed of 2 to 12 amino acids". It is unclear what unrecited additional components or steps, if any, are excluded from the scope of the claim (MPEP 2111.03).

b) Claims 18 and 19 are indefinite for the recitation "host animal cells producing the single chain Fv" as it is unclear whether host animal cells can naturally produce the scFv or whether the cells are "transfected" with an expression vector or plasmid encoding the scFv.

***35 USC § 103(a)***

18. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kontermann et al. (USPN 6,759,518; published July 6, 2004; filed April 9, 1999; hereinafter referred to as "Kontermann") in view of Mahler et al. (Immunotechnology 3:31-34 (1997); hereinafter referred to as "Mahler").

Claims 18 and 19 are drawn to methods for expressing a dimer from a single



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chain Fv where an animal host cell cultured under serum-free conditions, expresses the scFv and the dimer is produced in the medium, where the VH and VL regions for each scFv are connected by a linker comprising 2-12 amino acids.

Claims 18 and 19 were prima facie obvious at the time of the invention over Kontermann in view of Mahler.

Kontermann discloses recombinant dimers comprising a VH and VL domain connected by a peptide linker (L) in the form of a VH-L-VL construct or VL-L-VH construct, with the linker being as short as possible, preferably about 1-20 amino acids in particular about 1-5 amino acids, long (Col. 5, lines 28-34); methods for producing secreted dimer by introducing expression vectors encoding the construct(s) into an animal host cell including a yeast, insect or mammalian cell and cultivating the cell under expression conditions (Col. 8, line 13-64); suitable mammalian cells for expressing recombinant proteins (e.g., CHO or BHK cells, also a lymphocyte, a macrophage, a glia cell, an epithelial cell, a liver cell, a kidney cell, a bone marrow cell, an endothelial cell, a smooth or striped muscle cell or a fibroblast (Col. 9, lines 41-46). Kontermann does not disclose cultivating the host cells in serum-free medium.

Applicant's specification teaches "serum-free medium employed in the invention may be any medium conventionally used for the production of a recombinant protein without limit thereto" (p. 23, lines 3-5). Thus the limitation that the cell be grown in serum-free medium is not unique to the instant claimed method for producing or stabilizing dimers, but would have been obvious to one of ordinary skill at the time of the invention who wanted to express any recombinant protein. Mahler teaches expression

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of recombinant Fab or scFvs and their assembly into functional antibodies when expressed by mammalian cells cultured under serum-free conditions (Abstract; p. 33, Col. 2, ¶3). Mahler teaches that even though viable cell number is lower under serum free conditions, antibody titers in continuous subculture were similar (p. 38, Col. 2, ¶1).

One skilled in the art at the time of the invention would have been motivated and been assured of reasonable success in producing the instant claimed invention based on the disclosures of Kontermann in view of Mahler. Kontermann teaches forming dimers wit scFv by including a peptide linker comprising 2 to 12 amino acids in length occurring between the VH and VL of each scFv and culturing animal host cells transfected with expression constructs under conditions for expressing the scFv dimer, and Mahler discloses the advantages of growing transfected cells under serum-free culture conditions in order to express an antibody and provides an example of a protein-free serum formulation (e.g., S-2897). Mahler teaches that higher specific Mab rates have been reported in serum-free hybridoma cultures, suggesting that culture of cell lines in media with low FCS supplementation, or protein-free media formulations, may be beneficial with respect to both specific antibody productivity as well as facilitating purification (p. 42, Col. 1, ¶2 - Col. 2, ¶1). One skilled in the art would have been motivated to have combined the reference disclosures and could have done so in view of the availability of the cloning and cell culture technology and reagents in order to produce a method of instant claims 18 and 19. Thus the claims were prima facie obvious at the time of the invention over Kontermann in view of Malher.

Applicant is reminded that because the claims recite "comprising" language, that

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a linker comprising 2 to 12 amino acids (of any composition or sequence identity) would be encompassed by and thereof obvious over Kontermann.

### ***Conclusion***

13. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

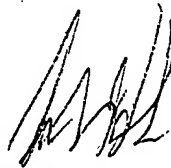
15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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**LARRY R. HELMS, PH.D.**  
**SUPERVISORY PATENT EXAMINER**